EXHIBIT I

UROGYNECOLOGY

Reanalysis of a randomized trial of 3 techniques of anterior colporrhaphy using clinically relevant definitions of success

Lauren Chmielewski, MD; Mark D. Walters, MD; Anne M. Weber, MD, MS; Matthew D. Barber, MD, MHS

OBJECTIVE: The purpose of this study was to reanalyze the results of a previously published trial that compared 3 methods of anterior colporrhaphy according to the clinically relevant definitions of success.

STUDY DESIGN: A secondary analysis of a trial of 114 subjects who underwent surgery for anterior pelvic organ prolapse who were assigned randomly to standard anterior colporrhaphy, ultralateral colporrhaphy, or anterior colporrhaphy plus polyglactin 910 mesh from 1996–1999. For the current analysis, success was defined as (1) no prolapse beyond the hymen, (2) the absence of prolapse symptoms (visual analog scale ≤2), and (3) the absence of retreatment.

RESULTS: Eighty-eight percent of the women met our definition of success at 1 year. One subject (1%) underwent surgery for recurrence 29 months after surgery. No differences among the 3 groups were noted for any outcomes.

CONCLUSION: Reanalysis of a trial of 3 methods of anterior colporrhaphy revealed considerably better success with the use of clinically relevant outcome criteria compared with strict anatomic criteria.

Key words: anterior colporrhaphy, cystocele, outcome measure, pelvic organ prolapse, treatment success

Cite this article as: Chmielewski L, Walters MD, Weber AM, et al. Reanalysis of a randomized trial of 3 techniques of anterior colporrhaphy using clinically relevant definitions of success. Am J Obstet Gynecol 2011;205:69.e1-8.

Approximately 200,000 women undergo surgery for pelvic organ prolapse (POP) annually in the United States, at an estimated cost of >$1 billion.[1] The anterior vaginal wall is the most common segment of the vagina to prolapse and is the segment that is most likely to fail long-term after surgical correction.[1] Anterior colporrhaphy has been used for the past century as a surgical technique to correct anterior vaginal prolapse. However, few randomized trials have evaluated the relative success of this technique.[2]

EDITORS' CHOICE

A randomized trial that compared 3 different methods of surgical correction of anterior vaginal prolapse was conducted between 1996 and 2001 by Weber et al.[3] A PubMed search of anterior colporrhaphy trials from 1979 to the present revealed that this was the first controlled clinical trial to compare different techniques of anterior colporrhaphy for prolapse repair. The study found that, at 23 months of follow up, patients with 70% of the traditional anterior colporrhaphy, 54% of the "ultralateral" anterior colporrhaphy, and 58% of the absorbable mesh-augmented colporrhaphy had recurrent descent of the anterior vaginal wall to within 1 cm of the hymenal ring (POP-quantification [POP-Q] stage 2 prolapse), although most patients were asymptomatic. No statistically significant difference in outcomes was noted among the 3 groups.[3] This trial has been cited frequently in the literature since its publication (196 citations; Scopus search Oct. 4, 2010) and, given the relatively low success found in the trial, often has been used as evidence that anterior colporrhaphy should either be augmented by synthetic mesh or another approach used (eg, sacrocolpopexy) for treatment of anterior vaginal prolapse.[4-8]

The definition of *success* that was used in the trial was based on recommendations of the 2001 National Institutes of Health (NIH) Workshop on Standardization of Terminology for Researchers in Pelvic Floor Disorders.[9] The workshop noted that these definitions were made arbitrarily and without the benefit of adequate knowledge of the epidemiology and natural history of POP or the relationship between anatomic support and pelvic floor symptoms. Since this workshop, advances in research have revealed these purely anatomic definitions to be too strict, because >75% of women who had annual gynecologic examinations without symptoms of POP would not meet the definition of "optimal anatomic outcome" and almost 40% of the women would not meet the definition of "satisfactory anatomic outcome."[10] Thus, studies that use even the NIH "satisfactory" anatomic outcome as their definition of treatment success, such as the trial in this analysis, classify a substantial number of women within the spectrum of normal anatomy as treatment failure.

Moreover, recent evidence suggests that the absence of vaginal bulge symptoms after surgery has a significant rela-

From the Obstetrics, Gynecology and Women's Health Institute, Cleveland Clinic, Cleveland, OH.

Presented at the 31st Annual Scientific Meeting of the American Urogynecologic Society, Long Beach, CA, Sept. 29-Oct. 2, 2010, and the joint Annual Meeting of the International Continence Society and the International Urogynecological Association, Toronto, ON, Canada, Aug. 23-27, 2010.

Received Dec. 13, 2010; revised Feb. 17, 2011; accepted March 14, 2011.

Reprints not available from the authors.

Authorship and contribution to the article is limited to the 4 authors indicated. There was no outside funding or technical assistance with the production of this article.

0002-9378/free

doi: 10.1016/j.ajog.2011.03.027

For Editors' Commentary, see Table of Contents

tionship with a patient's assessment of overall improvement; anatomic success alone does not.[11] As such, the National Institute of Child Health and Human Development (NICHD) Pelvic Floor Disorders Network has recommended that (1) any definition of success after POP surgery should include the absence of bulge symptoms in addition to anatomic criteria and the absence of retreatment and (2) the use of the hymen as a threshold for anatomic success seems a reasonable and defensible approach.[11] The objective of this study was to use the existing data that were collected by Weber et al[3] to reanalyze the results of the trial with these contemporary definitions of *success after prolapse surgery* to provide clinically relevant estimates of treatment effect for the 3 techniques that were used in the trial.

Materials and Methods

This is a secondary analysis of the clinical trial performed by Weber et al.[3] This trial was performed in the Department of Obstetrics and Gynecology at the Cleveland Clinic between June 1996 and January 2001; all of the original case report forms were reviewed, and the data were abstracted for this reanalysis. When pertinent data were not present on the original data-collection forms, the medical records were reviewed to obtain the missing data when available and included any data on retreatment or anatomic or subjective failure at time points beyond that in the original study. Study subjects were not recontacted for this analysis.

Subjects were included in the trial if they underwent operation for anterior vaginal prolapse at the Cleveland Clinic from June 1996 to May 1999 and provided institutional review board–approved informed consent. Patients were excluded if they underwent any incontinence procedure other than suburethral plication (Burch colposuspension, sling, or needle suspension). Based on clinical parameters determined by the urogynecologist, women with either no incontinence or mild or latent incontinence were eligible for participation in the study. Concurrent procedures for prolapse did not prohibit participation and did not affect group assignment.

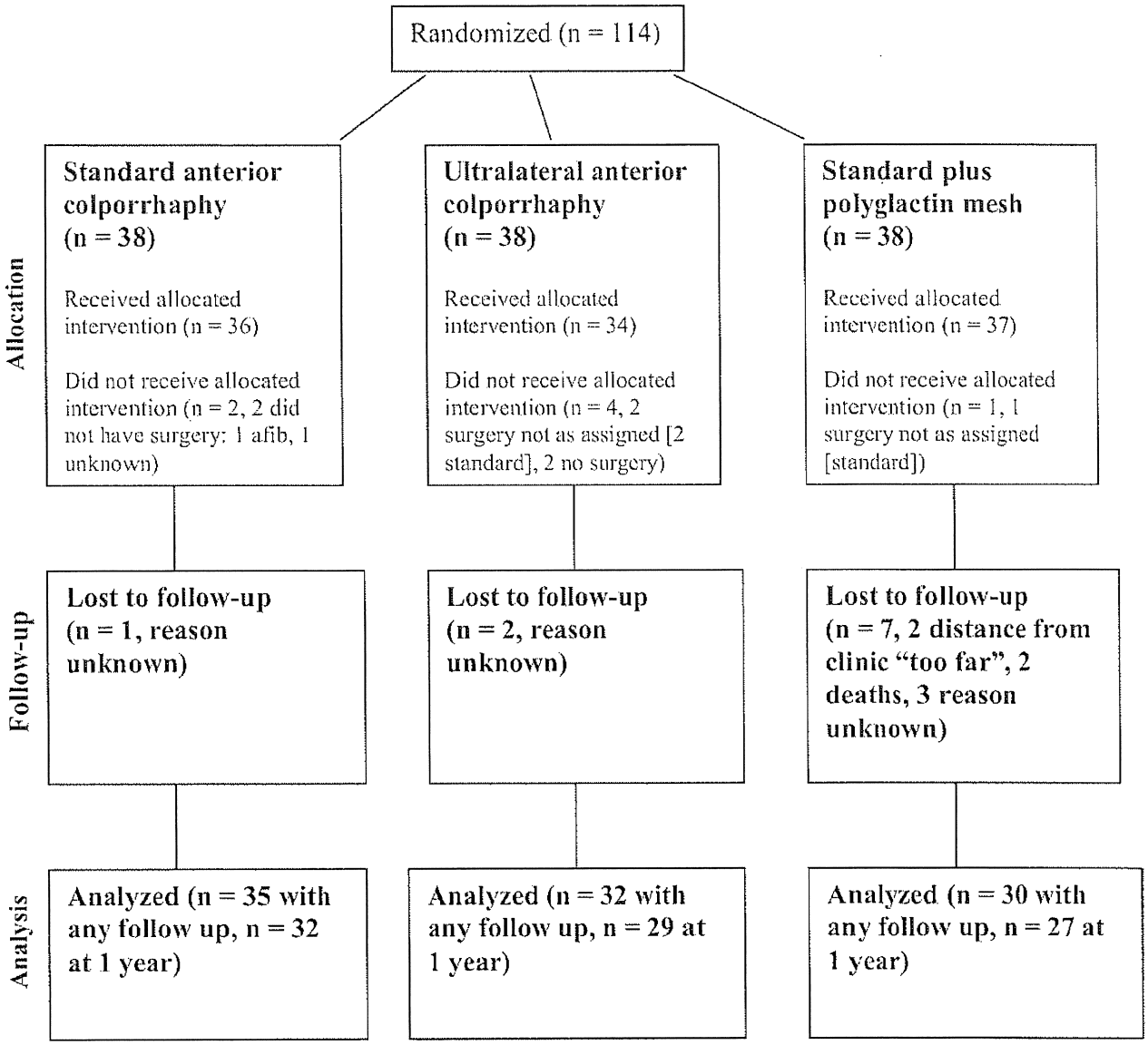
One hundred fourteen patients were assigned randomly (1:1:1) to 1 of 3 surgical techniques for anterior vaginal prolapse with the use of a computer-generated random numbers table: standard anterior colporrhaphy (n = 38), ultralateral colporrhaphy (n = 38), and standard anterior colporrhaphy plus mesh (n = 38). Patients completed questionnaires about prolapse symptoms and underwent physical examination before and after operation at approximately 6 months, 1 year, and 2 years. Visual analog scales (VAS; 0-100 mm) were used to assess the presence or absence of various pelvic floor symptoms. The POP-Q staging system was used to assess pelvic organ support; all POP-Q examinations were performed by a blinded examiner.[12] Data that were collected from intraoperative evaluation included physical examination, type of bladder neck plication, associated procedures, and any relevant complications. Further details of inclusion, data collection, and the randomization process can be found elsewhere.[3]

The original publication sought to determine whether there was a difference in the cure of anterior vaginal prolapse among the 3 different surgical techniques of anterior colporrhaphy. *Stage of prolapse* was defined at point Aa, point Ba, and the most advanced prolapse at any vaginal site. The primary outcome of anatomic success was defined as optimal when both points Aa and Ba were at stage 0 (-3 cm). Outcome was satisfactory when both points Aa and Ba were at stage 1 (≤–2 cm) and improved from preoperative staging. Cure was defined as either optimal or satisfactory anatomic outcome. Failure or unsatisfactory outcome was when either point Aa or Ba were >–2 cm.

In this reanalysis, we used outcome measures of treatment success that recently have been recommended by the NICHD Pelvic Floor Disorders Network.[11] Our *primary outcome was anatomic success* as defined by POP-Q measurements Ba, Bp, and the most dependent part of the vagina at ≤0 cm. At follow-up examination, subjects completed a prolapse symptom VAS: "How much are you bothered by symptoms related to vaginal prolapse?" (range, 0 [not at all] to 100 [extremely]). A priori, we defined *clinically relevant prolapse symptoms* as VAS of >20 mm. This cut-point was chosen rather than 0 because VASs are known to have end-aversion bias, at which respondents are often unwilling to mark extreme health states on continuous scales and because the VAS has been shown to have an imprecision of ± 20 mm on postoperative evaluations.[13,14] *Retreatment success* included the absence of retreatment (including pessary use or surgery for treatment of POP) within 40 months after surgery. For the analysis of the primary outcome of anatomic success (Ba, Bp, and most dependent part of the vagina at ≤0 cm), patients were analyzed in the group to which they had been assigned randomly (intention-to-treat analysis). Only subjects with prolapse beyond the hymen (Ba, Bp or C >0 cm) before surgery were included in our analysis of anatomic outcomes, which resulted in the exclusion of 2 subjects who provided postoperative anatomic data in the original analysis. Unlike the original study, all other outcomes (absence of bulging symptoms, retreatment/reoperation) were also analyzed according to randomization group. To minimize the impact of missing data, our primary analysis assessed treatment success at 1 year. For subjects without 1-year data but with follow-up evaluation beyond 1 year, we used the last-observation-carried-backward method for imputation.[15] Group comparisons of baseline and demographic characteristics were made with χ^2 or Fisher's exact tests for categoric factors; *t* tests or Wilcoxon rank sum tests were used for continuous factors, as appropriate. Because of differences in follow-up time in the primary outcome measure, the Kaplan-Meier method was also used to estimate the proportion of successes at follow-up evaluation and the log-rank test for comparison of success. This study was originally powered to detect a 30% difference among groups with 80% power and alpha of .05. Given that no sig-

FIGURE 1

Flow diagram of subject enrollment and follow-up evaluation



Afib, atrial fibrillation.

Chmielewski. Reanalyzing anterior colporrhaphy trial. Am J Obstet Gynecol 2011.

nificant differences were noted among groups in the original trial, we did not anticipate finding differences between groups for this analysis. As such, the primary analysis was performed on all subjects in aggregate to determine the overall proportion of subjects who experienced anatomic recurrence beyond the hymen, symptomatic recurrence, or required retreatment. Between-group comparisons were also performed, however.

RESULTS

A flowchart of subject enrollment and follow-up evaluation that was used for this analysis is shown in Figure 1. Of the 114 patients who were assigned randomly, 7 patients did not receive the allocated intervention. Four patients did not undergo operation (preoperative atrial fibrillation, 1 patient; reason unknown, 3 patients), and 3 patients had surgery that was not as assigned (2 patients from the ultralateral group and 1 patient from the standard plus mesh group had standard anterior colporrhaphy instead). Overall, follow-up data were analyzed for 35 patients in the standard group, 32 patients in the ultralateral group, and 30 patients in the standard plus mesh group.

The demographic and clinical characteristics of the 114 patients who underwent randomization (intention-to-treat

TABLE 1
Demographic and clinical characteristics

Characteristic	Standard (n = 38)	Ultra lateral (n = 38)	Mesh (n = 38)	Overall (n = 114)
Age, y[a]	65.4 ± 11.5	66.4 ± 7.7	62.9 ± 12.9	64.9 ± 10.9
Parity, n[b]	3 (0–10)	3 (1–10)	3 (1–8)	3 (0–10)
Menopausal status, n/N (%)				
Premenopausal	4/38 (10.5)	2/38 (5.3)	7/38 (18.4)	13/114 (11.4)
Postmenopausal with hormone therapy	16/38 (42.1)	21/38 (55.3)	13/38 (34.2)	50/114 (43.9)
Postmenopausal, no hormone therapy	18/38 (47.4)	15/38 (39.5)	18/38 (47.4)	51/114 (44.7)
Race, n/N (%)				
African American	2/38 (5.3)	1/38 (2.6)	3/38 (7.9)	6/114 (5.3)
White	36/38 (94.7)	37/38 (97.4)	33/38 (86.8)	106/114 (93)
Other	0/38	0/38	2/38 (5.3)	2/114 (1.8)
Body mass index, kg/m^2[b]	25.3 (18.2–36.5)	27.1 (17–36.9)	26.8 (17.4–44.4)	26.7 (17–44.4)
Current smoker, n/N (%)	15/38 (39.5)	11/38 (29)	13/38 (34.2)	39/114 (34.2)
Previous hysterectomy, n/N (%)	18/38 (47.3)	19/38 (50)	17/38 (44.7)	54/114 (47.4)
Previous prolapse operation, n/N (%)				
Abdominal or retropubic	2/37 (5.4)	2/38 (5.3)	2/38 (5.3)	6/113 (5.3)
Vaginal prolapse repair	3/37 (8.1)	3/37 (8.1)	3/38 (7.9)	9/112 (8)
Median preoperative pelvic organ prolapse, cm[b]				
Ba	2 (–2 to +8)	1.5 (–2 to +7)	3 (–2 to +7)	2 (–2 to +8)
C	0 (–7 to +10)	–4 (–10 to +7)	–0.5 (–12 to +8)	–2 (–12 to +10)
Bp	–1 (–3 to +8)	0 (–2 to +7)	–1 (–3 to +7)	–1 (–3 to +8)
Preoperative prolapse symptoms: visual analog scale >20 mm, n/N (%)	29/33 (88)	33/37 (89.2)	31/37 (84)	93/107 (86.9)

[a] Data are given as mean ± SD; [b] Data are given as median (range).

Chmielewski. Reanalyzing anterior colporrhaphy trial. Am J Obstet Gynecol 2011.

analysis) are shown in Table 1. There were no statistically significant differences among patients in the 3 study groups. At entry, median measures for POP-Q points were Ba = +2 cm (range, –1 to +8 cm), C = –2 cm (–12 to +10 cm), and Bp = –1 cm (–3 to +8 cm). Preoperative prolapse symptoms (VAS >20 mm) were present in 93 of 107 women (86.9%). Table 2 shows perioperative data for each group. In addition to anterior vaginal prolapse repair (n = 110), other procedures that were performed included vaginal hysterectomy (n = 57; 51.8%), posterior colporrhaphy (n = 100; 90.9%), enterocele repair (n = 29; 26.4%), and vaginal vault suspension (n = 50; 45.5%).

Ninety-seven subjects returned for at least 1 follow-up visit, with a median follow-up period of 26 months (range, 0–172 months). Table 3 shows 1-year outcomes. There were no significant differences in median POP-Q values between the groups at 1 year. Maximum descent of the anterior vaginal wall (point Ba) was a median of 1 cm proximal to the hymen (range, –3 to +4 cm), and the vaginal apex (point C) was 6 cm proximal to the hymen (range, –10 to +4 cm) with no differences between treatment groups. Overall, 67 of 75 patients (89%) who returned for follow-up examination had no prolapse beyond the hymen at 1 year, with no significant differences among groups. Ninety-five percent of patients (80/84 women) with 1-year follow-up examination denied prolapse symptoms, with no differences among groups. One patient from the mesh group had surgery for recurrent bulging symptoms at 29 months (vaginal vault suspension and enterocele repair). Overall, 112 of 113 women (99%) did not require retreatment for prolapse during the study follow-up period. Eighty-eight percent of the study population (66/75 women) with relevant follow-up data had no prolapse beyond the hymen, no prolapse symptoms, and no retreatment at last follow-up evaluation, which met our definition of surgical success.

Figure 2 shows the time-to-event data for each of the aforementioned outcome measures for the overall study population. The overall rates of anatomic success, subjective success, and no retreatment at 30 months with survival analysis was 82.3%, 93.9%, and 97.1%, respectively. The proportion of subjects who had no prolapse beyond the hymen, no prolapse symptoms, and no retreatment

TABLE 2
Concurrent procedures

Characteristic	Standard	Ultralateral	Mesh	Overall
Hysterectomy				
Total abdominal hysterectomy	1/36 (2.8)	0/36	0/38	1/110 (0.9)
Total vaginal hysterectomy	16/36 (44.4)	20/36 (55.6)	21/38 (55.3)	57/110 (51.8)
Vaginal vault suspension				
Iliococcygeus	15/36 (41.7)	17/36 (47.2)	14/38 (36.8)	46/110 (41.8)
Sacrospinous	1/36 (2.8)	0/36	2/38 (5.3)	3/110 (2.7)
Uterosacral	1/36 (2.8)	0/36	0/38	1/110 (0.9)
Posterior colporrhaphy	31/36 (86.1)	32/36 (88.9)	37/38 (97.4)	100/110 (90.9)
Enterocele repair	11/36 (30.6)	9/36 (25)	9/38 (23.4)	29/110 (26.4)
Abdominal colpopexy	1/36 (2.8)	0/34	0/38	1/108 (0.9)
Sling or Burch	0/36	0/34	0/38	0/109 (0)
Retropubic paravaginal repair	0/36	0/36	2/38 (5.3)	2/110 (1.8)

Data presented as n/N (%).

Chmielewski. Reanalyzing anterior colporrhaphy trial. Am J Obstet Gynecol 2011.

at this time point was 81.5%. No differences among groups were noted.

Comment

The success of surgery for POP can vary dramatically, depending on the definition of treatment success that is used.[11] A recent study that evaluated 18 different criteria for treatment success in patients who underwent abdominal sacral colpopexy enrolled in the CARE trial found that treatment success varied from 19% (POP-Q stage 0) to 97.2% (no retreatment for prolapse) with different success criteria.[11] The definition of success that was used originally in the trial by Weber et al[3] (POP-Q points Aa and Ba ≤−2 cm) is consistent with the 2001 NIH Standardization Workshop's recommendation that POP-Q stage 0 or 1 represented "satisfactory" anatomic outcomes. With the use of these original criteria, the success of anterior colporrhaphy ranged from 30-46%, depending on the surgical technique that was used.[3] Many interpreted the findings of that trial to indicate that the success for this common procedure was unacceptably low. This study has been cited frequently in original research articles, review articles, and book chapters as justification for the augmentation of anterior prolapse repairs with synthetic or biologic mesh or the use of another route of surgery (eg, sacral colpopexy) for treatment of anterior vaginal prolapse.[4-8] However, it has become increasingly clear that the NIH Workshop's anatomic criteria are too strict and may not represent clinically relevant criteria for treatment success after prolapse surgery. In this reanalysis, we sought to determine the success of

TABLE 3
Outcomes at 1 year

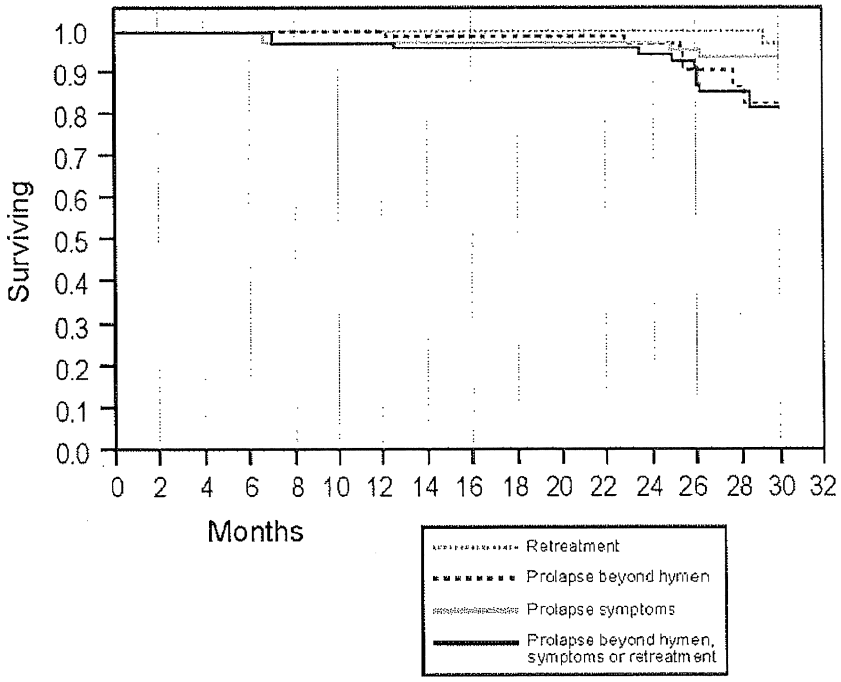
Variable	Standard	Ultralateral	Mesh	Overall
Pelvic organ prolapse quantification value, cm[a]				
Ba	−1.5 (−3 to +1)	−1.3 (−3 to +4)	−1 (−3 to +2)	−1 (−3 to 4)
C	−6 (−9 to +1)	−6 (−10 to +4)	−6 (−7.5 to −2.5)	−6 (−10 to 4)
Bp	−3 (−3 to +1)	−2.5 (−3 to +4)	−3 (−3 to 0)	−3 (−3 to 4)
No prolapse beyond the hymen, n/N (%)	25/28 (89)	20/24 (83)	22/23 (96)	67/75 (89)
Absence of pelvic organ prolapse symptoms, n/N (%)	32/32 (100)	27/29 (93)	21/23 (91)	80/84 (95)
No reoperations for pelvic organ prolapsed, n/N (%)	38/38 (100)	37/37 (100)	37/38 (97)	112/113 (99)
No prolapse beyond hymen, no symptoms, no retreatment, n/N (%)	25/28 (89)	20/24 (77)	21/23 (91)	66/75 (88)

All comparisons, $P > .05$.

[a] Data are given as median (range).

Chmielewski. Reanalyzing anterior colporrhaphy trial. Am J Obstet Gynecol 2011.

FIGURE 2
Kaplan Meier survival curves of time until failure of several treatment outcomes



The *dotted gray line* represents retreatment; the *dashed black line* represents prolapse beyond the hymen; the *solid gray line* represents prolapse symptoms; the *solid black line* represents prolapse beyond the hymen, symptoms, or retreatment.

Chmielewski. Reanalyzing anterior colporrhaphy trial. Am J Obstet Gynecol 2011.

anterior colporrhaphy for the treatment of anterior vaginal prolapse using clinically relevant, contemporary measures of success, rather than those used in the original publication.

Since the Workshop's recommendations were made, significant progress has been made in our understanding of the distribution of vaginal support in the general population, the relationship between pelvic organ support and various pelvic floor symptoms, and patients' perspectives of what constitutes a successful treatment outcome after surgery. We now know that 30-65% of women who receive routine gynecologic care have POP-Q stage II vaginal support on straining examination and therefore would not meet the Workshop's anatomic criteria for "satisfactory" treatment results.[10,16,17] Current evidence also suggests that the hymen is an important "cut-off point" for symptom development. Women with prolapse beyond the hymen have more pelvic floor symptoms and are much more likely to report "seeing or feeling a vaginal bulge" (the 1 symptom that best correlates with advanced prolapse) than women with prolapse at or proximal to the hymen.[18-21] Approximately 3-6% of women in the general population have prolapse beyond the hymen with straining, and a similar proportion have vaginal bulging symptoms.[10,16,22] Additionally, recent data indicate that, after surgical treatment, the absence of vaginal bulge symptoms has a significant relationship with a patient's assessment of overall improvement, with a patient's own assessment of treatment success, and with improvements in symptom bother and health-related quality of life; anatomic success alone does not.[11] Interestingly, it also appears that those women with perfect vaginal support (POP-Q stage 0) after the surgery have lower quality of life than those with lesser degrees of support, which suggests that some degree of vaginal relaxation or pliability is desirable for normal pelvic floor functioning.[13]

Using the currently available evidence, the NICHD Pelvic Floor Disorders Network has recommended that any definition of success after POP surgery should include the absence of bulge symptoms in addition to anatomic criteria and the absence of retreatment; use of the hymen as a threshold for anatomic success seems to be a reasonable and defensible approach.[11] We used these recommendations to develop the criteria for "clinically relevant treatment success" for this reanalysis. In this analysis, we found that anterior colporrhaphy that is performed in conjunction with traditional vaginal prolapse repairs results in anterior vaginal support that is not perfect (median Ba point; 1 cm). However, clinically relevant recurrence 1 year after surgery was relatively uncommon (12%): 11% of women experienced anatomic recurrence beyond the hymen; 5% of women experienced symptomatic recurrence, and none of the women required surgery for recurrence or complication in the first year. By way of comparison, clinically relevant recurrence after abdominal sacral colpopexy in the CARE trial that used the same criteria as in this analysis was 15% at 2 years, with 6% of the women experiencing prolapse beyond the hymen, 8% of the women experiencing symptomatic recurrence, and 3% of the women requiring retreatment.[11] Weber et al[3] considered only anterior vaginal support in their assessment of anatomic recurrence. In this analysis, we considered anterior, posterior, and apical segments in our criteria for anatomic success. Had we considered only the anterior vaginal segment (ie, anatomic success: Ba <0), the rate of anatomic success for the anterior wall would have been 92.2%.

Our findings are consistent with several recent randomized trials that compared anterior colporrhaphy with mesh-augmented vaginal repairs that found a relatively high proportion of women after anterior colporrhaphy who had stage II prolapse; however, the symptomatic cure was high, and reoperations were uncommon after a nonaugmented anterior

repair.[2] For instance, in a trial by Hiltunen et al[6] that compared anterior colporrhaphy with and without polypropylene mesh augmentation, the cure rate 12 months after surgery with the use of the NIH satisfactory anatomic outcome (POP-Q stage 0 or 1) was significantly higher after the mesh-augmented repair (93.3%) than the standard repair (61.5%; $P < .001$). However, the absence of vaginal bulge symptoms was noted in 94% and 93%, respectively ($P = .90$); the proportion with stage 3 or 4 prolapse was 3% vs 0% ($P = .11$), and reoperation for prolapse recurrence was 1% in each group. Thus, when strict anatomic criteria are used, mesh augmentation was superior to standard anterior colporrhaphy; no difference was seen for outcomes with clinical relevance. Of importance, women whose surgery was augmented with mesh more frequently had new onset stress urinary incontinence (22% vs 10%; $P < .02$) and mesh exposure (17% vs 0).[6] This highlights the need to balance surgical success, however measured, with adverse events to provide a full picture to patients during preoperative counseling. To date, no study that has compared anterior colporrhaphy with mesh-augmented repair has demonstrated a difference in terms of subjective success, quality of life outcomes, and reoperation for prolapse or incontinence.[2]

A surgeon's goal when correcting symptomatic POP is to resuspend the prolapsed vagina to provide anatomic support and symptom relief that is durable and results in normal pelvic floor functioning. Although we defined *anatomic success* in this study as no prolapse beyond the hymen, it is important to note that the long-term clinical relevance after surgery of asymptomatic vaginal descent that approaches, but does not go beyond, the hymen is unclear. If women with asymptomatic stage 2 prolapse after surgery are substantially more likely to progress over time to symptomatic recurrence and further surgery than women with stage 0 or 1 support, then early anatomic differences gain greater clinical significance; if the rate of symptomatic progression in this group is low, then the differences seen are less clinically meaningful.[11] Because of small sample size and a low rate of symptomatic recurrence in this trial, this analysis cannot provide insight into this issue. Surgical trials with long-term follow-up evaluation, particularly those with follow-up period of 5 to >10 years after surgery, are critical to determine the clinical relevance of this group.

Consistent with the low retreatment found in this analysis, Davila et al[23] reported reoperation in 3.4% for recurrent cystocele in a series of 207 cases of primary anterior colporrhaphy with or without other prolapse surgery after a median follow-up period of 50 months. A recent systematic review that examined complications and reoperations after traditional vaginal surgery, sacrocolpopexy, and vaginal mesh kits reported reoperation rate of 3.9% for prolapse after traditional vaginal repair that included a vault suspension (48 studies with mean follow-up period of 32 ± 20 months).[24] Although this is slightly higher than sacral colpopexy (2.3%) and vaginal mesh kits (1.3%), the follow-up period was the longest (32 ± 20 vs 27 ± 20 vs 17 ± 14 months, respectively), and complications were the lowest for this group. These low reoperation rates are encouraging; however, it should be emphasized that, although retreatment should always be considered a failure after prolapse surgery, the lack of retreatment by itself should not necessarily be considered a treatment success. Many patients with symptomatic and/or anatomic recurrence may forego repeat surgery and "live" with their symptoms to avoid the risk, discomfort, and inconvenience of repeat surgery. It is notable that only 45% of participants in this trial received a vaginal vault suspension, which was the conventional procedure at our institution at the time of this study (1996–1999). Although incompletely studied, consensus is growing that adequate support for the vaginal apex is an essential component of a durable surgical repair for women with advanced prolapse.[1,25-27] The Surgery for Prolapse Committee of the 4th International Consultation on Incontinence noted that "the apex is the keystone of pelvic organ support . . . the best surgical correction of the anterior and posterior walls is doomed to failure unless the apex is adequately supported."[25] Given this, it seems likely that clinically relevant recurrences after anterior colporrhaphy would be even lower than that found in this analysis if an adequate vaginal vault suspension was performed routinely, which is current practice for most reconstructive pelvic surgeons today.

The trial by Weber et al[3] had several limitations that also apply to this reanalysis. The sample size was small, which led to inadequate power to detect anything other than very large differences among the 3 treatment groups. Not surprisingly, as in the original trial, we found no significant differences in anatomic outcomes, symptoms, or retreatment among the study interventions in our analysis. The primary goal of this reanalysis was to provide estimates of clinically relevant treatment success for anterior colporrhaphy and not to compare different methods of anterior colporrhaphy or to evaluate the role of polyglactin mesh for the augmentation of anterior vaginal prolapse repair. One other clinical trial has evaluated the role of polyglactin augmentation with anterior colporrhaphy and demonstrated decreased anatomic recurrence with this absorbable synthetic mesh.[11] Combining the results of this trial with that of Weber et al,[3] the Cochrane Review on this subject concluded that standard anterior repair was associated with more recurrent cystoceles than when supplemented with a polyglactin mesh inlay (relative risk, 1.39; 95% confidence interval, 1.02–1.90), but data are lacking on morbidity and outcomes other than anatomic success.[2]

Another weakness of the trial by Weber et al[3] that applies equally to our analysis is the relatively high loss to follow-up evaluation and missing data in this study. To mitigate this as much as possible, we performed time-to-event analysis and focused our analysis on the 1-year data for which the data were more complete than with longer follow-up points and used a conservative imputation method (last observation carried backward) when possible. Using this approach and our predefined criteria, we

found overall treatment success of 88% for anterior colporrhaphy that was performed in conjunction with other traditional vaginal prolapse repairs. If all participants who were lost to follow-up were counted as treatment "successes," then the estimated cure would increase to 96 of 107 women (90%). If all participants who were lost to follow-up evaluation were counted as failures, success would fall to 66 of 107 women (62%). With time-to-event analysis to censor subjects who were lost to follow-up evaluation, the overall treatment success at 30 months was 81.5%. This study was also limited by the lack of validated pelvic floor symptom or quality-of-life questionnaires. At the time that the study by Weber et al[3] was performed, no such questionnaires for POP existed. Unlike many other studies that were performed in the same time frame that focused primarily on anatomic outcomes, this study did systematically assess a variety of pelvic floor symptoms that included prolapse symptoms with VAS. VAS have been demonstrated repeatedly to reliably measure symptom severity in a variety of conditions that include pelvic floor disorders[28,29]; for the purposes of this reanalysis, the VAS for prolapse symptoms seemed a reasonable approximation for the evaluation of vaginal bulging symptoms.

In conclusion, this study provides further evidence that success after prolapse surgery depends heavily on the criteria that are used to define treatment success. In the frequently cited study by Weber et al,[3] when strict anatomic criteria were used, success was low. However, when contemporary, clinically relevant criteria for success were used, treatment success was considerably better, with only 11% of subjects experiencing anatomic recurrence beyond the hymen, 5% of subjects experiencing symptomatic recurrence, and no subjects requiring surgery for recurrence or complications at 1 year. Given this and the excellent safety profile of traditional vaginal prolapse surgery, we conclude that anterior colporrhaphy that is performed in conjunction with other native tissue repairs is appropriate as a primary treatment of symptomatic anterior vaginal prolapse.

REFERENCES

1. Jelovsek JE, Maher C, Barber MD. Pelvic organ prolapse. Lancet 2007;369:1027-38.
2. Maher C, Feiner B, Baessler K, Adams EJ, Hagen S, Glazener CM. Surgical management of pelvic organ prolapse in women. Cochrane database Syst Rev 2010;4:CD004014.
3. Weber AM, Walters MD, Piedmonte MR, Ballard LA. Anterior colporrhaphy: a randomized trial of three surgical techniques. Am J Obstet Gynecol 2001;185:1299-306.
4. Feiner B, Gietelink L, Maher C. Anterior vaginal mesh sacrospinous hysteropexy and posterior fascial plication for anterior compartment dominated uterovaginal prolapse. Int Urogynecol J 2010;21:203-8.
5. Murphy M. Use of mesh and materials in pelvic floor surgery. Obstet Gynecol Clin North Am 2009;36:615-35.
6. Hiltunen R, Nieminen K, Takala T, et al. Low-weight polypropylene mesh for anterior vaginal wall prolapse: a randomized controlled trial. Obstet Gynecol 2007;110:455-62.
7. Ridgeway B, Chen CC, Paraiso MF. The use of synthetic mesh in pelvic reconstructive surgery. Clin Obstet Gynecol 2008;51:136-52.
8. Walters MD, Paraiso MF. Anterior vaginal wall prolapse: innovative surgical approaches. Cleve Clin J Med 2005;72(suppl 4):S20-7.
9. Weber AM, Abrams P, Brubaker L, et al. The standardization of terminology for researchers in female pelvic floor disorders. Int Urogynecol J Pelvic Floor Dysfunct 2001;12:178-86.
10. Swift S, Woodman P, O'Boyle A, et al. Pelvic Organ Support Study (POSST): the distribution, clinical definition, and epidemiologic condition of pelvic organ support defects. Am J Obstet Gynecol 2005;192:795-806.
11. Barber MD, Brubaker L, Nygaard I, et al. Defining success after surgery for pelvic organ prolapse. Obstet Gynecol 2009;114:600-9.
12. Bump RC, Mattiasson A, Bo K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol 1996;175:10-7.
13. Streiner DL, Norman GR. Health measurement scales: a practical guide to their development and use. Oxford, UK: Oxford University Press; 2003.
14. DeLoach LJ, Higgins MS, Caplan AB, Stiff JL. The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale. Anesth Analg 1998;86:102-6.
15. Horton NJ, Kleinman KP. Much ado about nothing: a comparison of missing data methods and software to fit incomplete data regression models. Am Stat 2007;61:79-90.
16. Swift SE. The distribution of pelvic organ support in a population of female subjects seen for routine gynecologic health care. Am J Obstet Gynecol 2000;183:277-85.
17. Trowbridge ER, Fultz NH, Patel DA, DeLancey JO, Fenner DE. Distribution of pelvic organ support measures in a population-based sample of middle-aged, community-dwelling African American and white women in southeastern Michigan. Am J Obstet Gynecol 2008;198:548.e1-6.
18. Barber MD. Symptoms and outcome measures of pelvic organ prolapse. Clin Obstet Gynecol 2005;48:648-61.
19. Bradley CS, Nygaard IE. Vaginal wall descensus and pelvic floor symptoms in older women. Obstet Gynecol 2005;106:759-66.
20. Swift SE, Tate SB, Nicholas J. Correlation of symptoms with degree of pelvic organ support in a general population of women: what is pelvic organ prolapse? Am J Obstet Gynecol 2003;189:372-9.
21. Tan JS, Lukacz ES, Menefee SA, Powell CR, Nager CW. Predictive value of prolapse symptoms: a large database study. Int Urogynecol J Pelvic Floor Dysfunct 2005;16:203-9.
22. Nygaard I, Barber MD, Burgio KL, et al. Prevalence of symptomatic pelvic floor disorders in US women. JAMA 2008;300:1311-6.
23. Davila GW, Ghoniem GM, Kapoor DS, Contreras-Ortiz O. Pelvic floor dysfunction management practice patterns: a survey of members of the International Urogynecological Association. Int Urogynecol J Pelvic Floor Dysfunct 2002;13:319-25.
24. Diwadkar GB, Barber MD, Feiner B, Maher C, Jelovsek JE. Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol 2009;113:367-73.
25. Brubaker L, Glazener C, Jacquetin B, et al. Surgery for pelvic organ prolapse. In: Abrams P, Cordozo L, Koury S, Wein A, eds. 4th International Consultation on Incontinence. Paris: Health Publication Ltd; 1273-1319.
26. Toozs-Hobson P, Boos K, Cardozo L. Management of vaginal vault prolapse. BJOG 1998;105:13-7.
27. Shull BL. Pelvic organ prolapse: anterior, superior, and posterior vaginal segment defects. Am J Obstet Gynecol 1999;181:6-11.
28. Rogers RG, Kammerer-Doak D, Olsen A, et al. A randomized, double-blind, placebo-controlled comparison of the effect of nitrofurantoin monohydrate macrocrystals on the development of urinary tract infections after surgery for pelvic organ prolapse and/or stress urinary incontinence with suprapubic catheterization. Am J Obstet Gynecol 2004;191:182-7.
29. Barber MD. Outcomes and quality of life measures in pelvic floor disorders. In: Walters MD, Karram MM, eds. Urogynecology and reconstructive pelvic surgery. St. Louis: Elsevier; 2005:497-512.